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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/331,204	08/20/1999	ROBERT TAM	216/013-US1	1379

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	PAPER NUMBER
1635	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	09/331,204	TAM, ROBERT	
	Examiner	Art Unit	
	James D. Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13 and 16-25* is/are rejected.

7)☒ Claim(s) *12,14 and 15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The language of claim 1 recites "An aptamer having a length of between about 12 and 22 nucleic acid units, inclusive, and a sequence which includes...". This claim could be read as claiming an aptamer having a length of... and also having a sequence..., or it could be read as claiming both an aptamer having a length of... and a separate sequence which includes the G-rich regions, leaving claim 1 and those dependent on it indefinite.

Claim 2, and 7-10 as recited in the original application are drawn to the aptamer of claim 1 wherein the G-rich regions "are separated by less than two to seven nucleotides..." The term "less than" implies a value lower than a single fixed point; the reference to a value lower than two fixed points as stated in the claim creates indefiniteness. Additionally, pre-amendment A attempted to address this by replacing the phrase "less than seven" of claim 2 with "by two to seven". However, the term "less than seven" doesn't appear in claim 2 or 7-10, invalidating this portion of the amendment and leaving the original claims unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is drawn to the aptamer of claim 2, wherein the immune regulatory protein is selected from the group of SP1, NFKB, EGR1, and AP2. This claim broadly encompasses not only said proteins, but any molecule which may potentially fall under the umbrella of such terms, such as fragments, homologues from any/all species, splice variants and alleles thereof. The specification of the instant application discloses only that SP1, NFκB, EGR1, and AP2 are immuno-regulatory proteins; no other definitions are provided for said acronyms, or descriptions given of structure, sequence, or specific function for any of the proteins mentioned above. Additionally, no disclosure of any interaction between an aptamer and any of NFκB, EGR1, or AP2 is provided that would lead one of ordinary skill in the art to believe applicant was in possession of the invention as claimed at the time of filing. Aptamer-mediated inhibition needs to be experimentally explored and is virtually impossible to determine *a priori*, given the high degree of variation and unpredictability in the field of oligonucleotide therapy. Since no other description of said proteins regarding their name, sequence, domain, motif, or specific function

are provided at all beyond the acronyms listed above, one of ordinary skill in the art could not properly envision said targets, and thus could not practice the invention as claimed.

Claims 17-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for aptamer-mediated inhibition of SP1 *in vitro*, does not reasonably provide enablement for aptamer-mediated methods of treating any disease associated with an inappropriate immune response *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The invention of the above claims is drawn to methods of treating a patient having a condition characterized by an inappropriate immune system response by administering an aptamer having at least two G-rich regions, wherein said condition may comprise a graft vs. host response, an autoimmune disorder, rheumatoid arthritis, multiple sclerosis, lupus, diabetes, or psoriasis.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using oligonucleotides in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of an oligonucleotide compound *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, such a disclosure would not be considered enabling since the state of oligonucleotide-

mediated protein inhibition is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of treatment using oligonucleotides.

A recent (2002) article by Braasch et al. identifies factors that contribute to the unpredictable efficacy of oligonucleotide compounds *in vivo*: difficulties with delivery to and uptake by cells of the oligonucleotides, toxicity and immunological problems caused by oligonucleotides, and artifacts created by unpredictable binding of oligonucleotide compounds to systemic and cellular proteins.

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378).

"[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379.

Braasch et al. discusses the non-specific toxicity effects of *in vivo* oligo administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense [oligonucleotide] mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense [oligonucleotide] effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense [oligonucleotide] drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column). Further, Branch reasons that "the value of a potential antisense [oligonucleotide] drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column).

While it is noted that the literature cited above focuses on antisense oligonucleotide treatment, the problems discussed herein are nevertheless generic to all forms of oligonucleotide therapy, since said complications arise solely from chemical structure which is indistinguishable between the two therapy forms. Thus, the specification of the instant application fails to provide

adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease as exemplified in the references above.

Further, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of SP1 *in vitro* as being correlative or representative of the successful *in vivo* aptamer-mediated treatment of any and/or all conditions or diseases suspected of being characterized by an inappropriate immune response. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of oligonucleotides in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by aptamer administration, and specifically regarding the methods claimed.

Said claims are drawn very broadly to methods of treating conditions or diseases suspected of being associated with an inappropriate immune response in humans. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for diseases or conditions suspected of being associated with an inappropriate immune response *in vivo*. Since the specification fails to provide any guidance for the successful treatment of any

and/or all diseases or conditions suspected of being associated with an inappropriate immune response in humans, and since determination of these factors for a particular immune regulatory protein in an organism is highly unpredictable, one of ordinary skill in the art would be unable to practice the invention as presented in the specification over the scope claimed.

Furthermore, the instant specification fails to provide one of skill in the art guidance for the selection of oligonucleotide compounds without undue trial and error experimentation since it is clear from the references above that in vitro and cellular screening do not correlate with oligonucleotide compounds that function in an *in vivo* environment. The specification in general fails to provide adequate guidance to overcome the obstacles and unpredictability of oligo therapy that are exemplified in the references above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 7, 9, and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Patel et al.

The invention of the above claims is interpreted as being directed to an aptamer between about 12 to 22 nucleotides wherein at least two G-rich regions exist, said G-rich regions selected

from the group consisting of GGnG, GGGG, GnGG, nGGG, and GGGn, wherein no directionality of said sequences is indicated. The invention is also drawn to said aptamer where the number of nucleotides separating each of the G-rich regions is 2 to 7, or 3 to 6, or where one of the at least two G-rich regions is comprises GGnG, GnGG, or GGGn wherein no directionality of said sequences is indicated.

Patel et al. teaches an aptamer in Fig. 1a that is an aptamer having several G-rich regions separated by 6 and 7 nucleotides, which are comprised of GnGG, GGnG, and GGGn.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharma et al. or Smith et al.

The invention of the above claims is interpreted as being directed to an aptamer between about 12 to 22 nucleotides wherein at least two G-rich regions exist, said G-rich regions selected from the group consisting of GGnG, GGGG, GnGG, nGGG, and GGGn, wherein no directionality of said sequences is indicated. The invention is also drawn to said aptamer where the number of nucleotides separating each of the G-rich regions is 2 to 7, or 3to 6, or 4, or where one of the at least two G-rich regions is comprises GGnG, GnGG, or GGGn, wherein said aptamer competes for the binding site of an immune regulatory protein which may consist of SP1, NFKB, EGR1 or AP2, wherein NFKB is assumed by the examiner to refer to NF Kappa B(NFκB).

Sharma et al. teaches an aptamer wherein the G-rich regions of said aptamer are between 2-7 nucleotides apart and acts on NFκB. Smith et al. teaches G-tetrad oligos wherein each tetrad is separated by four nucleotides.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 7-10, 11, 13 and 16 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3 and 4 of U.S. Patent No. 5,932,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims listed above embrace claims 3 and 4 of the previously issued patent.

Allowable Subject Matter

Claims 12, 14 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James D. Schultz, PhD
June 14, 2002